AMMONIUM SUCCINIMIDO-AURATE

A Gold Compound of Low Toxicity

M. E. OBERMAYER, M.D., and S. WILLIAM BECKER, M.S., M.D.[1]

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The latest extensive studies on the treatment of lupus erythematodes with gold compounds published in the United States are those of Wright (1), Throne et al. (1a) and Driver and Weller (2). Much attention has been paid to the problem in other countries, and a wealth of material has been accumulated which we shall briefly evaluate inasmuch as this has not been done in the foregoing studies. This task is facilitated by the publications of Fellner (3) and Leitner (4) who each in his field give an accurate résumé of our knowledge of the subject up to 1932 and 1934, respectively, with a comprehensive index of the literature. Hence, references included in these two papers will not be quoted.

Among the gold compounds which were more recently introduced, *Solganal B* has been used extensively in Europe, especially Germany. It has largely replaced the original Solganal because of its alleged lessened toxicity. Solganal B has only the trade-name in common with its predecessor; chemically it is entirely different. For while Solganal is the disodium salt of 4-sulphomethyl-amino-2-auro-mercaptophenyl-sulphonic acid, Solganal B is auro-thio-glykose ($C_6H_{11}O_5SAu$). In contrast to most of the other gold salts which are alkali compounds of aromatic acids, Solganal B is an aliphatic neutral derivative with a gold content of 50 per cent. Its toxicity is supposed to be 10 times less than that of Solganal; a guinea pig tolerated as high a dosage as 0.3 per kilogram. Solganal B is given subcutaneously or intramuscularly. The claim has been made (Hurch and Vonkennel (3)) that by administering the compound in an oily suspension the toxicity is further lessened. The slower resorption of gold suspended in oil has been demonstrated experimentally by Grassi (5). In this form Solganal B has been marketed under the trade-name of *Solganal B Oleosum* as a 2 per cent and a 20 per cent suspension.

[1] From the Section of Dermatology of the Department of Medicine, University of Chicago, Chicago, Ill.

Other compounds not included in Driver and Weller's study (2) are:

Aurosan, which is used mainly in Poland and is identical with Sanochrysin (Sodium Gold Thiosulphate). French equivalents of the latter are marketed under the name of *Crisalbine* and *Thiocrysine*. *Auroprotasin* is another gold preparation on which only a few reports have been published (6).

The Italian *Neocrisol*, a gold-arseno-benzol compound, and also *Fosfakrisol* and *Orotiol* the—latter also of Italian source.

Gold chloride ($AuCl_3$) which is given intravenously in a 1 per cent solution was elaborated in Germany and is also used in this country. Greenbaum (7), in this country, reports satisfactory results from the oral administration of gold sodium chloride.

Auro-Detoxin which contains 12.5 per cent gold. This allegedly non-toxic compound is considered by some investigators to be the best and safest gold preparation (Pillokat (8), Engel (9)).

Myochrysine (Gold Sodium Thiomalate) which contains 50 per cent gold.

Collaurin, which is a colloidal gold preparation containing 75 per cent gold and 25 per cent protective colloid (it is given by mouth).

Aurocollargol, which is a combination of gold and silver in a colloidal state (it is given intravenously). Gold content: 0.006 per cent. Silver content: 0.06 per cent. It is believed that the therapeutic effect of silver is increased by the gold.

Solutions of colloidal gold for intravenous administration are also marketed in this country by several pharmaceutical laboratories. However, sodium gold thiosulphate is the only gold compound which has been recognized by the Council on Pharmacy and Chemistry of the American Medical Association.

THERAPEUTIC USES

It can be said that in the chronic discoid form of lupus erythematodes gold has maintained its position as the treatment of choice, while it is contra-indicated in the acute and subacute forms of the disease. The only dissenting voice from this axiom is that of Bechet (in discussion of Engman (10)) who states that gold therapy is successful even in the acute forms of lupus erythematodes if extreme caution is used. Knowles (in discussion of Engman (10)) claims that gold is well tolerated in acute lupus erythematodes if given in the form of blood from a donor who had two hours before received an intravenous injection of 100 mg. of a gold preparation. Whether the minute amount of gold thus given has any specific effect remains to be determined.

The French tendency of recent years to prefer bismuth to gold has not yet been generally accepted, but is constantly gaining ground everywhere (Jordan and Tarabuchin (11), Srokowska (12)). In this country bismuth treatment has been favorably reported on by Ingels (13). Satisfactory treatment results by local injections of gold as inaugurated by Traub (14) were obtained by Gougerot and Burnier (15). Gougerot and Patte (16), however, warn against the possibility of anaphylactic and humoral shock which they experienced in the use of this method. The statement of Levin (17) that injection of gold directly into the lesion not only led to the cure of the lesion but also the disappearance of tubercle-bacilli in the sputum will have to be interpreted as a coincidence rather than a causal effect. Our own experiences with this method were not favorable. Whether the subcutaneous injection-method of Alden and Jones (18) (who used a stable, buffered solution) offers any definite advantage remains to be seen.

Treatment with gold compounds in the various forms of the tuberculids has also met with success. Good results with gold alone have been published by many investigators (3) in the treatment of erythema induratum Bazin, (tuberculosis indurativa), papulo-necrotic tuberculids and acnitis (tuberculosis papulo-necrotica) Boeck's sarcoid (latest report by Bureau et al. (19)) and lichen scrophulosorum (tuberculosis lichenoides). Erythema induratum seems to respond especially well.

It is agreed by the majority of investigators that in *true tuberculosis* of the skin gold therapy alone is insufficient. The tuberculous lesion may disappear under the treatment, but the development of tuberculous manifestations in other organs cannot be prevented (3); there is even a possibility of activation of latent tuberculous foci in other organs by gold-therapy (20). Yet the results obtained by the combination of other orthodox therapy plus gold administration have proven the efficacy of gold as an adjunct in lupus vulgaris (Fellner (3), Nicolas et al. (20)). Koga (21) and Epstein (22) have reported favorably on the treatment of lupus disseminatus faciei with gold preparations.

The use of gold compounds in treating tuberculosis of the lungs, and in the therapy of syphilis, and of leprosy, is beyond the scope of this paper. It may, however, be mentioned that an increasing number of other diseases has been subjected to treatment with gold. For example, *Erysipelas* has been successfully treated with Solganal (3); in *pyodermas* Solganal B has given good results (23); and *lymphogranuloma inguinale* was reported cured by the same compound (8, 24, 25).

Moreover, *arthritis deformans* (26) and gonorrhoic arthritis (27) have been treated successfully with gold and it seems that gold is also being used more and more in this country for chronic arthritis.

For the sake of completeness it should be mentioned that in general attempts which have been made to treat acne vulgaris (28) and psoriasis (1a, 29, 30) with gold compounds have not been successful. Throne and Myers (30a) claim that gold treatment for psoriasis is not only of practically no value but that it is contraindicated in this condition because of a decided tendency to reactions. Epstein et al. (22), however, report satisfactory results in acne, especially acne indurata. It is equally surprising to hear of good results in the treatment of parapsoriasis (31). Since no form of therapy has thus far proven effective in this obstinate dermatosis of unknown origin, the method seemed worth testing. Following Gougerot's suggestion we subjected two cases of pityriasis lichenoides chronica to prolonged treatment with ammonium succinimido-aurate but were unable to observe any change in the eruption. The favorable reports on the treatment of *lichen planus* (32, 33) are numerically insignificant in the face of the overwhelming number of reports on lichen planus produced by gold therapy (see skin-phenomena).

SKIN- AND MUCOUS-MEMBRANE PHENOMENA AS SEQUELAE OF GOLD THERAPY

The early reports mention many toxic phenomena even including deaths; and later authors have added a host of new and diversified observations (Fellner, 3).

In the more recent literature the following cutaneous disorders have been

reported: Erythroderma (34, 35, 36), generalized erythroderma following subcutaneous injections (37), desquamation of feet and hands without erythema (38), grave cutaneous and mucous membrane phenomena including persistent total alopecia (39), dermatitis (40, 41), exfoliative dermatitis (42, 43, 44), eczematoid dermatitis of the seborrhoic type (45), gold eczema (46).

Four cases of *keratoderma* from gold therapy are reported (Irgang, 47, Roxburgh, 48). In one patient, traces of gold could be demonstrated in the keratoderma blenorrhagica-like lesions. In another case, the keratoderma was associated with *melanoderma*. This seems to be the only report in the literature where a primary melanoderma,—i.e., hyper-pigmentation without relation to a preexisting eruption—has developed from the use of a gold compound. Gougerot and Carteaud (3) observed a retiform pigmentation. Touraine and Voillemin (49) a pigmentation "en nappes," Sézary et al. (50) a diffuse melanoderma. These pigmentations, however, appeared at sites previously occupied by the gold dermatitis, or erythroderma, respectively.

An interesting phenomenon, to which increased attention has been paid is the pigmentation resulting from the deposition of gold in the skin, first reported by Hansborg (3). Similar pigmentations from sanochrysin were observed by Zimmerli and Lutz (3), Lopez (3), and, later on—from chrysalbine—by Josserand (3), Gaté (3), Charpy (3), Cuilleret (3), Gougerot et al. (51), Touraine and Voillemin (49), Sézary et al. (52), Rathery et al. (53). It seems to be more frequently encountered in women, and—logically—patients with chrysiasis (gold pigmentations) usually show no symptoms of intolerance to gold (54). Cascos (55) has found that the difference between argyria and chrysiasis is only physical in nature. The silver particles are of uniform size and comparatively small, the gold particles less uniform and larger. Stillians, in his excellent report on argyria (56), does not consider chrysiasis in differential diagnosis. Since the clinical aspect of the two conditions is practically the same, and the biospectric method at present not simple enough to be possible for the practising dermatologist, it will be of interest to see whether the intradermal injection of reducing fluid offers a differential-diagnostic test between chrysiasis and argyria. In either chrysiasis or argyria the discoloration is often most evident upon the parts of the skin which are exposed to light, as has been reported by Sallman (57), Bernard et al. (58), Ramel (59), Cascos (60), and Fowler (61); the deposition may also be present in the tissues of the eyes (conjunctiva and cornea—Sallman, 57). Lorenzen (3) had 28 cases of chrysiasis among 57 patients who were treated with sanochrysin for tuberculosis of the lungs. He claims that the appearance of the pigmentation depends upon the total amount of gold administered. No patient developed pigmentation who had received a total dose of no more than 5 cg. per kilo but every patient who had been given 15 cg. per kilo developed chrysiasis towards the end of the first year after treatment. The intensity of the pigmentation reaches its peak during the second or third year.

The biospectrometric studies of the quantitative distribution of gold in the body, as carried out by Gaul and Stand (62), represent a far more accurate method of determining the minimum amount of gold which must be deposited in order to produce the clinical picture of chrysiasis.

An explanation for the mechanism of chrysiasis is offered by Sallman (57): Precious metals can be reduced easily; this reduction process is facilitated by

the effect of intense exposure to ultra-violet light. Bernard and his co-workers (58) found their three patients with chrysiasis sensitive to ultra-violet light. Negret (63) sensitized the skin to light by means of intravenous injections of Solganal. Gouin (64) goes so far as to assume that the action of ultra-violet light is indispensable for the therapeutic effect of gold since the gold-salts are activated in the body by ultra-violet light. In reference to this it may be remarked that Franck (65) reports the cure of a patient with lupus erythematodes of the face by the combination of gold-treatment and intensive local irradiations with ultra-violet light. In view of the generally acknowledged damaging effect of ultra-violet light, statements like these seem surprising and further investigations will be necessary to confirm or reject this theory.

The histo-chemical demonstration of gold has been accomplished many times (Timm, 66, Policard et al., 67, Gerlach et al., 68, Bernard et al., 58, Prüsener, 69, Hornus and Krassnoff, 70, Yamamato et al., 71, Gaul and Staud, 62) by staining as well as by spectroscopic methods. Fischl and his coworkers (72) and Feldt (73) have demonstrated gold in spirochetes and in trypanosomas. While the former authors regard these findings as a proof of the direct chemo-therapeutic effect of gold, the latter disproves this theory and claims that gold has no parasitotrophic effect but increases the natural defense forces. Feldt found that normal gold-sensitive spirochetes and gold-fast spirochetes both take up the same amount of gold. That gold has no bactericidal effect on cultures of tubercle-bacilli is reported by Courmont and his co-workers (74). Hornus and Krassnoff (70) found that gold collects in tuberculous foci and believe that the effect of gold therapy depends upon the presence of the metal in the diseased tissue where the fight between the acid-fast bacilli and the reticulo-endothelial cells is taking place. In this connection, the observation of Milian (75) who reported the occurrence of a so-called "perifocal" erythema from gold therapy, localized mainly in old and new tuberculous lesions, as well as that of Nicholas and Rousset (76) who observed purpuric lesions confined to the area of the healing lesions of lupus erythematodes, is interesting.

Among the manifold varieties of skin eruptions due to gold treatment one group deserves special attention, namely the toxic eruptions resembling *infectious diseases*. The close similarity between scarlatina and gold dermatitis with exanthem was pointed out by Laporte (77). Further observations led French investigators to believe that these eruptions are not toxic (allergic) phenomena but represent the infectious disease which they resemble. This is explained by activation of latent organisms ("biotropisme" of Milian). In this country, Keim (77a) has given an excellent report on the subject. In the case of gold therapy such "Aurides biotropiques" may be produced by the same organism for which the gold was administered, e.g., papulo-necrotic tuberculids in patients under treatment for tuberculosis (the occurrence of tuberculids and of eruptions simulating tuberculids has frequently been reported, see Fellner (3)) or dissemination of lupus erythematodes in patients treated for the chronic discoid form (direct biotropism). Or, they may be produced by latent organisms the existence of which was not known, e.g., measles in patients under treatment for lupus erythematodes or scarlatina in patients under treatment for arthritic conditions ("indirect biotropism"). Milian (78) recently observed the development of icterus in a syphilitic patient while under gold treatment. He inter-

preted the syphilitic icterus as another example of indirect biotropism. Asdéry (79) who has reported on the subject claims that the characteristics for biotropic phenomena consist in the acute appearance on the ninth day, the clinical aspect, the fact that spontaneous involution will take place in spite of the continuation of gold treatment and the negative reaction to intradermaltests with gold.

Whether or not the hypothesis of biotropism will be substantiated, the fact remains that some gold eruptions present a differential diagnostic problem in regard to certain infectious diseases. Also peculiar to gold (and, incidentally, to bismuth) seems to be the imitation (?) of pityriasis rosea. Kiess and Strandberg reported one such case from Aurophos (3), Konrad one from Lopion (3) and our own observations (see page 97) confirm their experiences.

Lichen planus seems to be the most common eruption attributable to gold therapy (80, 81, 49, 82, 84, 85, 86, 87, 88, 89, 90). The lichen eruption may also assume the form of *lichen corneus, verrucosus,* or *spinulosus* (91, 92, 93, 93a). At this point we wish to add a pertinent experience of our own:

A patient with lichenoid lupus erythematodes under treatment with sodium gold thiosulphate developed an eruption in the form of lichen spinulosus. Thus it seems that the individual reaction to various harmful agents in general remained constant as far as the localization is concerned. The reaction to both, to the unknown agents responsible for the lupus erythematodes and to the gold, became and remained follicular. It is not a mere speculation if we assume that this patient would have responded to other agents in the same particular way, e.g., in the form of Bockhart's impetigo to a streptococcic infection or in the form of a follicular seborrheic dermatitis, had he been subject to these affections. J. Jadassohn's observations of follicular syphilids and follicular reactions to tuberculin frequently occurring in the same patients seem to support this hypothesis.

Sometimes the gold eruption presents a mixture of lichen planus and psoriasis (82, 94, 83). Dermatitis herpetiformis has also been observed (26).

An interesting observation of a peculiar localization of gold dermatitis is reported by Gougerot and Boucher (95): the areas involved were the ones exposed to light and the sites of a previous dermatitis medicamentosa on the legs. Pillsbury's (96) report on gold dermatitis in a patient with vitiligo, in whom the gold dermatitis was limited to the depigmented skin is another example of the unknown mechanism involved in the localization of reactions, and perhaps due to the effects of light.

The situation as to the value of skin testing is still uncertain (97). Flandin and his co-workers (98) believe that epidermal tests make it possible to differentiate between eruptions due to individual sensitivity to gold and those of a merely "toxic" nature. The statement of Gougerot and Degas (99) who claim that polyvalent sensitivity to foods developed following erythroderma from gold does not convince us in regard to proof of causal connection. Our experience also disagrees with that of Lichtenstein (100) in regard to the value of patch tests in dermatoses due to gold. We believe that further progress will have to be made in the allergy problem as a whole before practical conclusions can be drawn.

Of the attempts at desensitization, the method of Dainow (101) who claims that by administration of ascorbic acid (vitamin C) signs of intolerance including erythroderma can be overcome, deserves attention.

Dissemination of chronic lupus erythematodes by gold treatment which—

according to Milian—would have to be interpreted as a biotropic rather than a toxic effect, has been observed many times (1, 2, 3, 102, 103, and our own observations. See p. 94). The differential diagnosis between new lesions in the dissemination of chronic lupus erythematodes and the lesions of a medicamentous gold eruption sometimes becomes a difficult problem, and microscopic examination may be necessary to make the decision.

Involvement of the *mucous membranes of the mouth* is frequently associated with cutaneous phenomena and may sometimes precede the cutaneous eruption. The lesions are usually diffuse. Tenderness is present. Salivation is, as a rule, not increased (Lebeuf and Mollard, 3). But bullous stomatitis (Gate, 104) and ulcerative forms with necrosis (Kohrs, 3, Kren, 3, Gougerot and Blum, 105, Flandin et al., 106) have also been reported. Milian (107) gives a review of the clinic and therapy of gold stomatitis. Other reports are by Gougerot and Burnier (83), Hallbaur (108), and Cordiviola (109). Isolated lichen planus of the buccal mucous membrane was reported by Mohrmann (86), Schneidering (110), and by Hölzer (111). Gold keratosis of the mouth was described by Szanto (112). Systemic manifestations referable to internal organs resemble in general those seen following the arsphenamines. It seems that reports of serious damage to the internal organs have become relatively less frequent (Fellner, 3). Renal damage has been reported lately by Kallo (113) and by Stopcryk (114). Lombardo (115) has found that the first sign of a beginning auronephrosis is the finding of the epithelial cast consisting of "cellule auriche."

Damage to the hemato-poietic system occurs not infrequently. *Agranulocytosis* (Achard et al. 116, Ameuille and Braillon, 117, Margarat et al., 118, Chabaud et al., 119, Ellman and Lawrence, 120) may develop even from the use of gold compounds which do not contain a benzene ring (Dameshek, 120a). Up to the present, however, no damage to the hemato-poietic system could be produced in rabbits by the administration of gold (121).

The purpuric syndrome with fatal outcome has been reported by Achard et al. (116), Fortunato (122), Vigne (123), and Cremer (124). Emile et al. (125) have collected 30 cases of hemorrhagic disturbances. Further observations are reported by Gougerot and Blum (126), Bie (127), Silveira (128). Intoxication with blood changes may occur in spite of small doses (Armand-Delille et al., 129, Gougerot and Patte, 130). It is claimed by Gouin (131) that leukocytosis on the second day following the first injection of gold is diagnostic for the presence of tuberculosis, a statement which awaits confirmation.

Involvement of the *respiratory organs* seems to be a rare occurrence. Core (132) reports on rhino-pharyngo-stomatitis and edematous laryngitis, Coste et al. (133) on gold bronchitis. The latter, being of the Milian school, interpret the bronchitis as a biotropic phenomenon (see page 97).

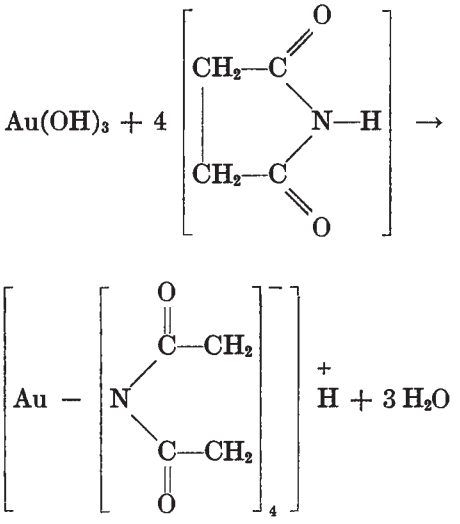
Damages to the *nervous system* are fortunately rare. Hemiplegia, paralysis of the radial nerve, and polyneuritis have been reported (3, 134). Of interest is the loss of the sensory phenomenon of taste which followed immediately after the injection (Solganal) and persisted for 6 weeks. Provocation of a recurrent polyradiculitis was reported by Chavany and Bourdillon (135). A fatal case of bulbar asphyxia associated with erythroderma from gold was observed by Pierre-Bourgeois et al. (136). Tuberculous meningitis following gold treatment (Lebeuf and Mollard, 137) will have to be interpreted as a biotropic phenomenon (see page 97).

CHEMICAL CHARACTER AND TOXICITY OF SUCCINIMIDO GOLD COMPOUND

The above review demonstrates that cumulative experience indicates that there are significant hazards involved in gold-therapy, particularly intravenous therapy.

However, considerable progress in the chemistry of organic gold compounds has been made in recent years (Kharasch and Isbell (138, 139, 140, 141), Kharasch and Beck (142)). It was with the hope of finding a gold compound more satisfactory than sodium gold thiosulphate that this study was undertaken.

We decided to investigate at first a new class of organic gold compounds prepared by Kharasch and Isbell (141), namely the gold compounds of succinimide. These investigators record that gold hydroxide reacts with succinimide in the presence of a small amount of a halogen salt or mineral acid to yield a complex in which the gold has a coordination number of four



It is very remarkable that the free "imido auric acids" (as these compounds are called) are very strong acids and will form stable ammonium, sodium and other salts. The salts yield colourless solutions characterized by great stability toward both heat and

reducing agents—a unique property for organic gold compounds. Ammonium succinimido aurate may be crystallized from hot glacial acetic acid without decomposition.

Crystalline ammonium succinimido-aurate is a white powder and has the following empirical formula: $NH_4Au(C_4H_4O_2N)_4 \cdot 4H_2O$. The water of crystallization may be removed by drying the substance in an evacuated vessel over phosphorus pentoxide. The compound is somewhat soluble in water. The presence, however, of other salts, particularly salts of halides such as sodium chloride, increases the solubility.[2] The toxicity of the compound was determined and found to be remarkably low for a gold compound. Thus, one gram of the substance produced no toxic symptoms in a rabbit of 3 kg., a result which stands in marked contrast to the high toxicity of sodium gold thiosulphate. In our investigation a fresh solution was made for every patient. The material was dissolved in boiling water, allowed to cool, and administered intravenously. No definite concentration for therapy was adopted. It varied with the individual dosage used. The extreme limits of concentration employed were 0.005 to 1.0 gram of the substance in 5 to 10 cc. of physiological salt solution. Recently, in order to decrease the amount of water used for injection, the more soluble sodium salt of the imido-auric acid was employed. This salt contains 28.4 per cent of gold and 8.6 per cent of nitrogen. A single dose of 300 mg. per kilogram of weight is well tolerated by rabbits and guinea pigs. A dose of 500 mg. per kilogram weight proved fatal within 5 days and gold was demonstrated in most of the vital organs. Because of the superior solubility and its low toxicity, the sodium succinimido aurate was exhaustively studied and submitted for the approval of the Council on Pharmacy and Chemistry.

In order to evaluate this compound clinically, it was thought desirable to compare its clinical effectiveness and toxicity with that of sodium gold thiosulphate. Furthermore, since lupus erythematodes is the condition wherein gold treatment has its greatest present applicability, it was decided to study the suc-

[2] The material for our study was prepared for us by Dr. Ben C. Sher of the Municipal Tuberculosis Sanatorium of Chicago.

cinimido gold compound primarily in the treatment of this disease.

CLINICAL DATA

Our clinical studies extended to the use of the succinimido aurates in the treatment of lupus erythematodes, lupus vulgaris, and other forms of skin tuberculosis.

In the ten years of operation of the University Clinics a total of 117 patients with various forms of lupus erythematodes and of cutaneous tuberculosis have come under our observation. These we have classified as follows:

1. Lupus erythematodes in its various forms	86
2. Lupus miliaris disseminatus faciei	2
3. Lupus erythematoides of Leloir	1
4. Lupus vulgaris	7
5. Papulo-necrotic tuberculid	13
6. Erythema induratum	8
	117

Since our extensive study of succinimido aurates was primarily directed toward the treatment of lupus erythematodes, it is of importance to classify further forms of this condition which came under our observation, as well as other pertinent clinical data.

Total number of lupus erythematodes patients

Acute form	4
Subacute form	10
Chronic discoid form	61
Edematous form	7
Classification uncertain	4
	86

Sex

32 male, 54 female

Age

Under 5 years	0
Between 6 and 15	4
Between 16 and 25	12
Between 26 and 35	30
Between 36 and 45	23
Between 46 and 55	10
Over 56	7
Total	86

Location

Face	67
Ears	9
Scalp and hairline	15
Neck	8
Chest	4
Back	2
Trunk	1
Arms	6
Hands	3
Legs	0
Lips	10
Mucous membranes of mouth	4
Mucous membranes of genitalia	0
All mucous membranes	1

Definite clinical foci of infection

Tuberculosis of lungs	6
Tonsils	8
Teeth	10
Gallbladder	1[3]
Kidney	1[3]
Prostate gland	1
Arthritis	3

Of the 86 patients, 13 received no treatment, some because they were referred only for diagnosis and some because of refusal to take treatment. The remaining 73 patients received the mode of treatment which by itself, or in combination with other methods, seemed to be indicated in the individual case. The following chemical compounds were used:

Ammonium and sodium succinimido-aurate by intravenous injection (49 cases).

Quinine sulphate by mouth (in all acute cases, in the subacute cases as a preparatory phase of treatment, and in the chronic recurrent forms during rest intervals between courses).

Sodium gold thiosulphate by intravenous injection.

Gold sodium chloride ($NaAuCl_4$) by intravenous injection.

Neo-silver-arsphenamine by intravenous injection.

Iodo-bismitol by intramuscular injection.

CO_2 snow locally (in case of non-response).

[3] The two cases of infected gallbladder and infected kidney showed spectacular improvement following cholecystectomy and nephrectomy respectively but recurrence followed subsequent acute infections (streptococcal sinusitis and cystitis, respectively).

CLINICAL RESULTS OF TREATMENT WITH SUCCINIMIDO GOLD COMPOUNDS AND SODIUM GOLD THIOSULPHATE

Following the usual custom, in writing this paper we prepared tables showing the number of patients who were improved, not improved, aggravated, etc. However, those familiar with the treatment of this tricky disease know the varied response of the individual patient with lupus erythematodes to any mode of treatment, the tendency to spontaneous involution in some cases, the uncontrollable tendency to recurrence in others. Moreover, a number of patients had been treated by several methods during the course of the disease; others came to us after they had been treated unsuccessfully with gold compounds elsewhere. Tabulation of such varied data may thus lead to a great deal of confusion, error in interpretation, and, sometimes may be definitely misleading. It was thought best therefore to omit tables. The following statement of our data and experience seems justifiable.

Under all conditions the gold succinimide compounds were as effective as the sodium gold thiosulphate although they seem to act somewhat more slowly.[4]

The contra-indications remain the same for both chemicals, namely, their use in the treatment of the acute disseminated form of the disease. It is our opinion that in this acute type treatment should be limited to bed rest and large doses of quinine by mouth.

Although of equal therapeutic effectiveness, the marked advantage of the succinimido-aurates over sodium gold thiosulphate consists in the paucity and mildness of the untoward reactions with succinimido-aurate. While severe reactions of the type recorded in the literature were observed with sodium gold thiosulphate, no severe reactions and only the following mild upsets were seen with the salts of succinimido aurates in the 49 patients under treatment.

Rise in temperature	1
Diarrhea	1

[4] This slower effect has perhaps found its explanation by recent excretion studies carried out by Dr. Ben C. Sher which will be published separately. It has been shown that far larger amounts of gold succinimides are excreted on the first day than of sodium gold thiosulphate. Therefore it might be advisable to give the injections twice a week instead of once a week in order to obtain a more rapid effect.

Slight nausea	2
Vomiting	2
Loss of appetite	1
Feeling tired	7
Headache	2
Abdominal pains	1
Flare-up of original skin lesions	2

Furthermore, the complete absence of dermatitis, erythroderma, exfoliative dermatitis, or purpura, is most striking. The only eruptions which were observed after gold succinimide therapy were the following:

One generalized macular eruption following the 4th injection.

One pityriasis-rosea-like eruption with lesions on the palms and on the mucous membrane of the mouth.

One pityriasis-rosea-like eruption which closely simulated ordinary pityriasis-rosea.

One erythematous, partly exudative eruption over the sternum and on the upper back.

It is most significant that in 3 of these cases the eruptions cleared up in from one to three months *in spite of continuation of the treatment with ammonium succinimido-aurate.* In the fourth case, the administration of the gold salt was temporarily stopped because of the possibility of acute dissemination of the patient's lupus erythematodes. The eruption disappeared slowly under treatment with quinine sulfate per os. Administration of ammonium succinimido-aurate was resumed and the patient has since shown no further skin manifestations attributable to gold therapy.

The interpretation of these few mild eruptions due to gold succinimide is difficult. Milian's school would probably interpret them as biotropic (see page 96). In any case, since treatment with the succinimido gold compound could be successfuly continued in spite of the presence of the eruption, if their nature was allergic, a long lasting desensitization or refractory phase must have been the rule. Patch tests on these four patients were negative to ammonium succinimido aurate as well as to sodium gold thiosulphate.

As to our general method of treatment of chronic lupus ery-

thematodes, we wish to state that we recognize two essential etiological factors which should be simultaneously combated in order to achieve best results.

The first is the infectious factor, which today is generally recognized regardless of whether the tubercle-bacillus, the streptococcus or any other bacterial agent is responsibe in the individual case. Thus far, most clinicians have been satisfied to treat lupus erythematodes symptomatically, i.e., until the disappearance of the lesions, and then to discharge the patient with the admonition to return if the condition should recur. Such an attitude is not unlike the one which prevailed in the old days regarding syphilis. If we are dealing with a chronic infectious disease as most investigators agree we are, it should be treated not symptomatically but rationally. We feel that the chronic lupus erythematodes patient is in a condition somewhat analogous to the syphilitic patient and should receive alternating courses of gold intravenously and of bismuth intramuscularly and rest periods during which he is given quinine-sulphate per os. How long this treatment should be continued to achieve permanent results will—and to cite again the analogy with syphilis—be a matter of experience, and it will take many years and a large amount of clinical experimental data for an unequivocal answer.

The second factor, of equal importance, is fatigue. Stokes in his discussion of Engman Jr.'s paper (10) has stressed a most suggestive combination of allergic reaction and chronic exhaustion which is commonly found in patients with lupus erythematodes. As a matter of fact one of us (S. W. B—143) has stressed for years the necessity of rest and relaxation in this disease and the present trend of recognition of this factor is encouraging. We wish to emphasize again the practical importance of this factor in the treatment of not only the acute and subacute forms of lupus erythematodes but in the chronic form as well.

CONCLUSIONS

1. The complex salts of the imido-auric-acids—in form of the ammonium or the sodium salt—represent gold compounds of

low toxicity suitable for intravenous therapy where gold treatment is indicated.

2. Their toxicity is much lower than that of sodium gold thiosulphate.

3. When used in lupus erythematodes they show a therapeutic effect similar to—but perhaps slower than—that of sodium gold thiosulphate.

4. In our experience untoward reactions from ammonium succinimido-aurate are much less frequent and certainly less serious than those from other gold compounds, particularly than those from sodium gold thiosulphate.

5. Serious cutaneous phenomena have not been observed from use of the new gold compound.

6. It is our opinion that the use of ammonium succinimido-aurate makes gold therapy a safer procedure for the patient and this gold compound is therefore recommended.

7. In chronic lupus erythematodes we recommend prolonged rational treatment in the form of alternating intravenous courses of gold and intramuscular bismuth injections, with interpolated rest periods during which the patient is given quinine sulphate by mouth. We recommend this method in place of the usual symptomatic treatment, which generally ceases as soon as the skin lesions have disappeared.

SUMMARY

The treatment of dermatoses with gold, its indications, contraindications and the toxic and allergic phenomena resulting from the administration of gold preparations are discussed.

Results are reported on the employment of ammonium succinimido-aurate, a new gold compound of low toxicity, in the treatment of 49 patients with lupus erythematodes The reported observations extend over a period of six years. Therapeutic activity is slower than with certain other gold compounds, such as sodium gold thiosulphate, but untoward reactions are less frequent and less severe. Serious cutaneous phenomena have never been observed. Ammonium succinimido-aurate is a valuable addition in the therapy of lupus erythematodes.

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